REMARKS

Reconsideration of this application is respectfully requested.

Claims 42-57 have been canceled. New claims 58-78 are derived from canceled claims 42-57. The amendment adds no new matter.

Rejections under 35 U.S.C. § 101

Claims 42-57 were rejected under 35 U.S.C. § 101 for allegedly lacking utility. Applicant traverses the rejection.

Contrary to the Examiner's assertion, the instant situation is not directly analogous to *Brenner v. Manson*. Unlike the situation in *Brenner*, Applicant's claimed nucleic acids are not simply "alleged to be potentially useful." Rather, Applicant's specification asserts specific, substantial, and credible utilities for the claimed nucleic acids. Accordingly, the Examiner's reliance on *Brenner* is misplaced.

Applicant's claimed invention fulfills the requirements of 35 U.S.C. § 101. Applicant's claims 58-67 recite isolated nucleic acids encoded by SEQ ID NO:3 and nucleic acids that hybridize to SEQ ID NO:3. Applicant's specification asserts a specific utility for these nucleic acids, namely, that all or a portion of the nucleic acids of SEQ ID NO:3, including oligonucleotides, can be used by those skilled in the art in well-known techniques to identify human chromosome 2, to analyze abnormalities associated with gene mapping to chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, and as a positional marker to map other genes of unknown location. (Specification at 37, lines 1-32.) This utility is specific, substantial, and credible.

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In Paper No. 17, the Office did not specifically respond to Applicant's arguments regarding this utility set forth in the Amendment and Response filed August 27, 2002. (Amendment at 2-5.) The Office had, however, previously taken the position that "this utility is not specific because many oligonucleotides share chromosomal localization and achieve similar results of serving as probes for mapping genes. Furthermore, the region of chromosome 2 that applicants point to as being the target of the instant nucleic acid, when used as a probe, is extremely large extending up to 92-110 megabases (see attached map view of chromosome 2q11-2q12) and many probes such as SEQ ID NO:3 would be equivalent to the instant probes." (Paper No. 12 at 6.) The Office's position is inconsistent with current legal precedent regarding the utility requirement of 35 U.S.C. § 101.

The U.S. Court of Appeals for the Federal Circuit has stated: "An invention need not be the best or the only way to accomplish a certain result, and it need only be useful to some extent and in certain applications." *Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d 1094, 1100 (1991). Therefore, Applicant's claimed nucleic acids do not need to be the best or only way to identify human chromosome 2, to analyze abnormalities associated with gene mapping to chromosome 2, to distinguish conditions in which this marker is rearranged or deleted, or to serve as a positional marker to map other genes of unknown location. Rather, Applicant's claimed nucleic acids need only be useful to some extent and in certain applications. Applicant's claimed nucleic acids fulfill this requirement.

The nucleic acids of claims 58-67 can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2. For example, the

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nucleic acids of claims 58-67 can be used in fluorescence *in situ* hybridization (FISH) studies to specifically detect chromosome 2, and to detect rearrangements associated with chromosome 2, such as duplications and triplications. These are credible "real world" utilities that can be practiced with applicant's invention without any need for any additional research.

As objective evidence of the "real world" utility of Applicant's DNAs, Applicant submits herewith Exhibits 1-6. These Exhibits provide objective evidence that the skilled artisan could use Applicant's claimed invention for the detection of chromosome 2 and for the detection of rearrangements associated with chromosome 2. In view of these Exhibits, the inescapable conclusion is that Applicant asserted a credible "real world" utility for IL-1 delta DNA in the specification.

Giardino et al. (Exhibit 1) analyzed a chromosomal rearrangement in a patient with psychotic illness and mild mental retardation. Giardino et al., at 319, col. 2, last full ¶. FISH was used to characterize a small supernumerary marker chromosome (SMC) found in the cells of the mother and child. *Id.* at 321, Fig 2. Giardino et al. determined that the SMC was derived from the proximal region of human chromosome 2. *Id.* at 321, Table 1. Several probes for 2q11.2 and 2q12 detected both the normal chromosomes and the SMC, whereas more distal probes for 2q12 detected only the normal chromosomes. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the SMC. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining

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the presence of normal chromosome 2 sequences and for characterizing the composition of the SMC described by Giardino et al.

Moreover, in Table 2, Giardino et al. provide a list of chromosome 2 partial trisomy cases and associated phenotypic findings. All of the trisomy cases appear to be associated with the proximal region of chromosome 2, which is the region to which Applicant mapped IL-1 delta DNA. Applicant asserted that IL-1 delta DNA can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2. (Specification at 37, lines 1-32.) The Office has not provided any reason to doubt that Applicant's DNA could be used to detect and characterize these cases of trisomy of the proximal chromosome 2 region. Such a use is a "real world" use.

As stated in Giardino et al., "FISH analyses using unique sequences are useful means of obtaining information about the euchromatic regions contained in a SMC and delineating new chromosomal syndromes, aimed to offer suitable genetic counseling, especially when an SMC is observed in prenatal diagnosis." Giardino et al. at 322, col. 2, first ¶. There can be no doubt that Applicant's unique DNA sequence would be useful in FISH analyses for obtaining information about the euchromatic regions contained in a SMC and delineating new chromosomal syndromes.

Riegel et al. (Exhibit 2) examined a patient with various abnormalities, and found an abnormal chromosome 2. Riegel et al. at 76, Abstract. Using FISH, they determined that there was a direct tandem duplication of 2q11-q13.2. *Id.* Several probes for 2q11.1-q13 detected a single signal on one chromosome and two signals on the abnormal chromosome. *Id.* at 78, Table 1. In contrast, a probe for 2q14 detected a

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single signal on both chromosomes. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the abnormal chromosome. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the duplicated region of chromosome 2 described by Riegel et al.

Riegel et al. indicate that the duplication was "identified with the help of fluorescence in situ hybridization studies using band-specific YAC probes." *Id.* at 76, col. 1-2, bridging ¶. Applicant asserted that IL-1 delta DNA can be used to detect human chromosome 2 and rearrangements or deletions associated with chromosome 2. (Specification at 37, lines 1-32.) The Office has not provided any reason to doubt that Applicant's DNA could be used to detect and characterize duplications of the proximal chromosome 2 region as described in Riegel et al. Such a use is a "real world" use.

Wang et al. (Exhibit 3) examined a fetus with various abnormalities, and found an abnormal chromosome 2. Wang et al. at 312, Abstract. Using FISH, they determined that there was a triplication of 2q11.2-q21. *Id.* Thus, probes mapping to the proximal region of chromosome 2 are useful for determining the presence of normal chromosome 2 sequences and for characterizing the composition of the abnormal chromosome containing the triplication. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the triplicated region of chromosome 2 described by Wang et al. Such a use is a "real world" use.

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Glass et al. (Exhibit 4) examined a patient with various abnormalities, and found an abnormal chromosome 2. Glass et al. at 319, Abstract. Using FISH, they determined that there was a proximal 2q trisomy (2q11.2-q21.1). *Id.* FISH showed an insertion of chromosome 2-derived material into the middle of the short arm of chromosome 8. *Id.* at 320, Figure 4. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the insertion of material derived from chromosome 2 into chromosome 8 described by Glass et al. Such a use is a "real world" use.

Mu et al. (Exhibit 5) examined a patient with various abnormalities, and found an abnormal chromosome 2. Mu et al. at 57, Summary. They determined that there was a tandem duplication of 2q11.2-q14.2. *Id.* *Id.* at 78, Table 1. Although Mu et al. did not perform any hybridization analyses, probes mapping to the proximal region of chromosome 2 would have been useful for determining the presence of normal chromosome 2 sequences on one of the chromosomes and for characterizing the duplicated region of the abnormal chromosome. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for characterizing the duplicated region of chromosome 2 described by Wu et al. Such a use is a "real world" use.

Reddy et al. (Exhibit 6) studied intrachromosomal triplications, including a triplication of 2q11.2-2q21. Reddy et al. at 134, Abstract. Reddy et al. states: "Triplications can be mistaken for duplications. Therefore, in assessing duplications, FISH confirmation is recommended." *Id.* Consequently, it is appreciated in the art that

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FISH is useful for assessing duplications and confirming triplications, including those involving the proximal region of chromosome 2. Since Applicant's DNA localizes to the proximal region of chromosome 2, it is useful as a probe for determining the presence of normal chromosome 2 sequences and for assessing duplications and confirming triplications involving the proximal region of chromosome 2. Such a use is a "real world" use.

Exhibits 1-6 provide evidence that, as Applicant asserted in the specification, the claimed nucleic acids can be used to identify human chromosome 2 and to distinguish conditions in which this marker is rearranged or deleted. In view of this evidence, it is indisputable that Applicant's claimed nucleic acids are useful at least "to some extent and in certain applications," which is sufficient to fulfill the utility requirement of 35 U.S.C. § 101. *See Carl Zeiss Stiftung v. Renishaw plc*, 20 U.S.P.Q.2d at 1100. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Furthermore, Applicant's claims 64-78 recite isolated nucleic acids that encode SEQ ID NO:4, fragments of SEQ ID NO:4, and polypeptides with at least 80% amino acid identity to SEQ ID NO:4; expression vectors comprising these nucleic acids; host cells comprising the expression vectors; and methods for producing polypeptides by culturing these host cells. Claims 64-78 contain the recitation that the polypeptide "binds to cells expressing an IL-1 delta receptor." Applicant asserted in the specification that IL-1 delta was useful for, among other things, purifying proteins, as delivery agents, and as therapeutic agents. (Specification at 39.) These utilities take advantage of the ability of IL-1 delta to bind to its receptor. These utilities are credible "real world" utilities.

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The specification teaches that IL-1 delta can be used to purify or identify cells that express an IL-1 delta counter-structure molecule. (*Id.* at 40-41.) This utility was based on the sequence of IL-1 delta polypeptide, its homology to other IL-1 family members, the responsiveness of the murine polypeptide to LPS and CD40L, and the expression pattern of human IL-1 delta. (*Id.* at 8-9.) There is no reason to doubt Applicant's asserted utilities. As shown by Debets et al. (*J. Immunol.*, 2001, 167:1440-1446), submitted with Applicant's Response filed August 22, 2002, binding of IL-1 delta to cells expressing IL-1 delta receptors is a measurable activity. Thus, Debets et al. provides evidence of the credibility of Applicant's asserted utility.

Moreover, the purification and identification of cells based on interactions with counterstructures on the cell surface was a well-known technique in the art at the time the application was filed. For example, von Schonfeldt et al. (Exhibit 7) showed that viable cells having the c-kit receptor protein on the cell surface could be analyzed and sorted based on interactions with an antibody on magnetic beads. von Schonfeldt et al. at 582, Abstract. von Schonfeldt et al. indicated that magnetic cell separation was a widely used method for separating many different types of cells, and that negative and positive selection strategies using depletion columns or positive selection columns had been implemented. *Id.* at 582, col. 1-2, bridging ¶.

Furthermore, LaCasse et al. (Exhibit 8) showed that cells expressing Shiga-like toxin-1 (SLT-1) receptors could be detected in flow cytometry using a FITC-labeled SLT-1 subunit. LaCasse et al. at 2902, col. 2, first ¶, and at 2904, Fig. 2.). Based on von Schonfeldt et al. and LaCasse et al., the skilled artisan would have expected that Applicant's IL-1 delta polypeptides could be used to identify and purify cells expressing

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an IL-1 delta counter-structure molecule, and that they could be used in negative and positive selection strategies. Moreover, based on these references, the skilled artisan would understand that these utilities are credible "real world" utilities.

In addition, on page 10, lines 5-7, of the specification, Applicant asserted that a soluble version of IL-1 delta may act as an antagonist of other, active cytokines, in the same way that IL-1ra is an antagonist of the actions of IL-1 alpha and IL-1 beta. Debets et al. (*J. Immunol.*, 2001, 167:1440-1446) found that IL-1 delta antagonizes the activity of another IL-1 family member, referred to therein as IL-1 epsilon, which activity is mediated by binding to a receptor referred to as IL-1R6 (a member of the IL-1 receptor family). Thus, Debets et al. provides evidence of the credibility of Applicant's asserted utility.

Moreover, IL-1 delta polypeptides are useful in the detection and removal of cross-reacting antibodies in preparations of polyclonal antisera against IL-1ra. Applicant determined that the amino acid sequence of human IL-1 delta has 50% identity with the amino acid sequence of IL-1ra. (Specification at 9, lines 22-26.) It was well-known at the time the application was filed that the proportion of cross-reacting antibodies in a polyclonal antiserum is dependent upon a number of factors, of which the degree of structural relatedness between the two antigens is of particular importance. J. W. Goding, *Monclonal Antibodies:Priciples and Practice*, Academic Press, pp 42-43, 1986 (Exhibit 9). Thus, the 50% identity between IL-1ra and IL-1 delta would be expected to result in some level of cross-reacting antibodies to IL-1 delta in polyclonal antisera against IL-1ra.

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In view of Applicant's discovery of a protein with 50% amino acid identity with IL-1ra, a skilled artisan using polyclonal antiserum against IL-1ra would have immediately recognized that the polyclonal antiserum could contain antibodies that cross-reacted with IL-1 delta, thereby decreasing the specificity of this antisera. For example, in Malyak et al. and Towbin et al. (Exhibits 10 and 11), polyclonal antisera were used detect IL-1ra. The skilled artisan would have recognized that the polyclonal antisera being used might contain a subpopulation of antibodies cross-reacting against IL-1 delta, and that the presence of cross-reacting antibodies might interfere with the specificity and accuracy of the assay.

Based on 50% identity of the amino acid sequence of human Il-1 delta with the amino acid sequence of IL-1ra, IL-1 delta polypeptides could be used to detect cross-reaction with polyclonal antisera against IL-1ra by routine immunological detection techniques, such as western blotting. Furthermore, IL-1 delta polypeptides could be used to remove the cross-reacting antibodies from a polyclonal antiserum against IL-1ra, for example, by absorption with IL-1 delta coupled to agarose beads or by passing the serum over a column of immobilized IL-1 delta. *See* Goding at 42 and 291. The unbound antiserum, having been depleted for antibodies that interact with IL-1 delta, would have enhanced specificity for IL-1ra. These are credible "real world" utilities for IL-1 delta polypeptides.

As discussed above, Applicant's specification asserts numerous credible "real world" utilities. Applicants have provided herewith Exhibits 1-11, which provide objective evidence supporting Applicant's asserted utilities. The Office has provided no

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evidence to the contrary. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 42-57 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not having either a specific and substantial asserted utility or a well established utility for the same reasons set forth for the rejections under 35 U.S.C. § 101.

Applicant traverses the rejection. For the reasons detailed above, the skilled artisan would understand how to use the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 42-55 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for any nucleic acid molecule encoding a fragment of the polypeptide of SEQ ID NO:4 that has the ability to bind to cells expressing an IL-1 delta receptor. The Office concludes that Applicant's specification does not enable the skilled artisan to make the invention commensurate in scope with the claims. (Paper No. 17 at 6.) It is the Office's position that, without identification of specific residues critical for binding to an IL-1 delta receptor, undue experimentation would be required to determine which fragment, if any, of SEQ ID NO:3 would encode a fragment that will bind to the IL-1 delta receptor.

Applicant traverses the rejection. Applicant points out that new claims 58-63, similar to prior claims 56 and 57, are not limited to nucleic acids that encode a polypeptide that binds to cells expressing an IL-1 delta receptor. Rather, claims 58-63 encompass nucleic acids without regard to the ability of any encoded polypeptide to

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bind to cells expressing an IL-1 delta receptor. Consequently, none of the Office's reasons for non-enablement is relevant to claims 58-63.

With respect to claims 64-78, Applicant reiterates that screening for molecules cannot be equated with undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988). The Office has conceded that the skilled artisan could make the claimed molecules and screen for their binding. (Paper No. 12 at 10.) The fact that some screening, even a very large amount of screening, is required cannot serve as the basis for concluding that undue experimentation is required. *See In re Wands*, 8 U.S.P.Q.2d at 1406.

The Office has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). Moreover, a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Office has based its conclusion that undue experimentation would be required on its contention that the identification of residues critical for IL-1 delta binding is required for screening. However, the Office has provided no evidence to support this contention. If the Examiner is relying on information within her personal knowledge, Applicant requests that the Examiner submit an Affidavit under 37 C.F.R § 1.104(d)(2).

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In the absence of any evidence, the Office's conclusion that undue experimentation would be required is unsupported.

Furthermore, as shown by Debets et al., (*J. Immunol.*, 2001, 167:1440-1446), submitted with Applicant's Response filed August 22, 2002, binding to cells expressing an IL-1 delta receptor is a measurable activity. The evidence of record indicates that no undue experimentation would be required. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 42-55 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to the skilled artisan that the inventor had possession of the claimed invention at the time the application was filed. It is the Office's position that the specification only describes a nucleic acid of SEQ ID NO:3 and an encoded protein having the amino acid of SEQ ID NO:4, and fails to describe any other nucleic acid that lacks SEQ ID NO:3 and encodes a protein that has the activities possessed by IL-1 delta polypeptide.

Applicant traverses the rejection. Applicant points out that new claims 58-63, similar to prior claims 56 and 57, are not limited to nucleic acids that encode a polypeptide that binds to cells expressing an IL-1 delta receptor. Rather, claims 58-63 encompass nucleic acids without regard to the ability of any encoded polypeptide to bind to cells expressing an IL-1 delta receptor. Consequently, none of the Office's reasons for lack of an adequate written description is relevant to claims 58-63.

With respect to claims 64-78, Applicant provided the nucleotide and amino acid sequences of a complete IL-1 delta DNA (SEQ ID NO:3) and a complete IL-1 delta

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polypeptide (SEQ ID NO:4), and identified homologous proteins, such as IL-1ra. Moreover, as Applicant teaches in the specification, a given amino acid may be replaced by a residue having similar physiochemical characteristics. (Specification at 18, lines 12-18.) The specification also teaches that selected C-terminal amino acids may be deleted, and it teaches that selected N-terminal amino acids may be deleted. (Specification at 16, lines 12-17.) Based on this information, the skilled artisan would be able to envision numerous additional IL-1 delta variants.

As the Office has recognized, IL-1 delta exhibits high identity with IL-1ra and other IL-1 family members. (Paper No. 12 at 8.) As further recognized by the Office, for proteins whose sequence identity is above 30%, one can use homology modeling to build structure. (Paper No. 12 at 10, citing Skolnick et al.) Since all of the IL-1 family members are involved in modulating inflammation, the skilled artisan could compare the sequences of the IL-1 family members to predict likely positions within IL-1 delta that would not affect binding. Screening for binding activity of IL-1 polypeptides modified or deleted at these positions could be used to confirm these predictions. There is no evidence of record that that the identification of residues critical for IL-1 delta binding is required for Applicant's screening process. Based on Applicant's teachings, the skilled artisan would recognize that Applicant had possession of the claimed genus of IL-1 delta molecules. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Claims 52-55 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for a nucleic acid molecule that hybridizes to the coding sequence of SEQ ID NO:3 and encodes a

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polypeptide that binds to cells expressing an IL-1 delta receptor. The Office contends that there is no knowledge existing in the art or guidance in the specification for making a nucleic acid that encodes a specific polypeptide from an antisense strand.

Applicant traverses the rejection. In normal transcription and translation processes, an antisense DNA molecule is used as a template for transcription of a sense RNA molecule. The sense RNA molecule is then translated into a polypeptide. Thus, the antisense DNA molecule and sense RNA molecule encode the polypeptide. Accordingly, Applicant respectfully submits that the basis for this rejection is in error.

In addition, Applicant's new claims do not recite a nucleic acid molecule that hybridizes to the coding sequence of SEQ ID NO:3 and encodes a polypeptide that binds to cells expressing an IL-1 delta receptor. Accordingly, this rejection is moot.

Applicant submits that this application is in condition for allowance. If the Examiner should disagree, the Examiner is invited to contact the undersigned to discuss any remaining issues.

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